How to select a donor and product for allogeneic HCT
Dr Bronwen Shaw
10 February 2015
Overview

- Who (and where) are the donors

- What factors determine how we choose between them
  - Acquisition
  - Clinical

- Donor selection algorithms
The HLA Family

A1  A2
Cw7  Cw5
B8  B44

A3  A26
Cw7  Cw8
B7  B14

A1  A3
Cw7  Cw7
B8  B7

A1  A26
Cw7  Cw8
B8  B14

A2  A3
Cw5  Cw7
B44  B7

Barney

Be a match, save a life
The HLA Family

A1  A2  Cw7  Cw5  B8  B44

A3  A26  Cw7  Cw8  B7  B14

A1  A3  A1  A26  Cw7  Cw7  B8  B14  B44  B7

A2  A3  Cw5  Cw7  B8  B7

A1  A3  Cw7  Cw7  B8  B7

MTR INATIONAL BLOOD IPLANT RESEARCH

ANTHONY NOLAN
BE A MATCH, SAVE A LIFE
The HLA Family

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A2  A3
Cw5  Cw7

B8  B7

Be a Match, Save a Life
Bone Marrow Donors Worldwide
www.bmdw.org

- Total 25,092,358
  - 24,489,329 unrelated donors
  - 603,029 CBU
- 74 stem cell donor registries from 53 countries
- 49 cord blood banks from 33 countries
### Relative risks and benefits of different cell sources: acquisition issues

<table>
<thead>
<tr>
<th></th>
<th><strong>UD</strong></th>
<th><strong>Cord</strong></th>
<th><strong>Haplo</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HLA match</strong></td>
<td>90% Caucasian</td>
<td>Increased chance (esp rarer tissue types)</td>
<td>Almost always</td>
</tr>
<tr>
<td></td>
<td>16% ethnic minority</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Availability</strong></td>
<td>Variable Donor attrition</td>
<td>Relatively quick</td>
<td>Predictable</td>
</tr>
<tr>
<td><strong>Speed of acquisition</strong></td>
<td>Medium</td>
<td>Fast</td>
<td>Fast</td>
</tr>
<tr>
<td><strong>Cell dose</strong></td>
<td>Predictable</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>Quality</strong></td>
<td>Predictable</td>
<td>Unclear</td>
<td>Predictable</td>
</tr>
<tr>
<td><strong>Second donations</strong></td>
<td>Possible</td>
<td>Not possible</td>
<td>Possible</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>Higher than sibling</td>
<td>Much higher</td>
<td>Equal to sibling</td>
</tr>
</tbody>
</table>

*Note: UD typically refers to unrelated donors.*
Relative risks and benefits of different cell sources: clinical outcomes

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<tbody>
<tr>
<td>Engraftment</td>
<td>Fast</td>
<td>Slow</td>
<td>Fast</td>
</tr>
<tr>
<td>Graft failure</td>
<td>Rare</td>
<td>More common</td>
<td>Rare with new techniques</td>
</tr>
<tr>
<td>GvHD</td>
<td>High (esp with mismatch)</td>
<td>Lower than expected with mismatch</td>
<td>Low due to techniques</td>
</tr>
<tr>
<td>Relapse</td>
<td>Possibly lower than sibling</td>
<td>Possibly lower than sibling</td>
<td>Higher</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>Many recent studies show equivalence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Comparisons of clinical outcomes: UCB vs Haplo (BMT CTN 0603/0604)

Overall survival

- Haplo: 84%, 74%, 54%, 54%
- Cord: 68%, 52%, 46%, 39%

Progression-free survival

- Haplo: 40%
- Cord: 36%, 38%, 35%
Comparisons of clinical outcomes: RD vs UD vs Haplo

Adjusted estimated probabilities of (A) overall and (B) disease-free survival by donor type.

Bashey A et al. JCO 2013;31:1310-1316
Comparisons of clinical outcomes: RD vs UD vs mmUD vs UCB vs Haplo

Figure 4 Actuarial survival of patients stratified for donor type. Overall there is no statistically significant difference in survival.

Anna Maria Raiola, Alida Dominietto, Carmen di Grazia, Teresa Lamparelli, Francesca Gualandi, Adalberto Ibati...

Unmanipulated Haploidentical Transplants Compared with Other Alternative Donors and Matched Sibling Grafts

Biology of Blood and Marrow Transplantation, Volume 20, Issue 10, 2014, 1573 - 1579
Algorithm of donor search: historical

- HLA identical sibling donor
- (HLA matched unrelated donor)
- HLA mismatched unrelated donor
- Haplodidentical donor
Algorithm of donor search: 1990s

- HLA identical sibling donor
- HLA matched unrelated donor
- HLA mismatched unrelated donor
- UCB unit (s)
- Haploidentical donor
Algorithm of donor search: 1990s

- HLA identical sibling donor
- HLA (mis)mismatched unrelated donor
- HLA mismatched unrelated donor
- UCB unit (s)
- Haploidentical donor
Algorithm of donor search: today

HLA identical sibling donor

HLA matched unrelated donor

HLA mm unrelated donor

UCB unit (s)

Haplo donor
Algorithm of donor search: today

- HLA identical sibling donor
- HLA matched unrelated donor
- HLA mm unrelated donor
- UCB unit (s)
- Haplo donor

But it gets even more complicated…….
## Donor Selection Criteria

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<tbody>
<tr>
<td><strong>HLA match</strong></td>
<td>A, B, C, DRB1 (Maybe DQB1, DPB1)</td>
<td>A, B, C, DRB1 (LR/HR)</td>
<td>1 Haplotype</td>
</tr>
<tr>
<td><strong>Other genetic factors</strong> (e.g. KIR, NIMA)</td>
<td>Many, not routine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CMV serostatus</strong></td>
<td>Match</td>
<td>Negative</td>
<td>?</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Younger better</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>No difference in OS</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td><strong>ABO match</strong> (manipulation)</td>
<td>Controversial</td>
<td>Important</td>
<td>Important</td>
</tr>
<tr>
<td><strong>Antibodies</strong></td>
<td>Some importance</td>
<td>Likely important</td>
<td>Very important</td>
</tr>
</tbody>
</table>
Impact of HLA mismatches on OS: UD

Lee et al, Blood 2007; 110:4576-83

1454 patients
Impact of HLA mismatches on OS: UCB

Eapen M et al. Blood 2014;123:133-140
Impact of donor age on OS: UD

Impact of donor sex on OS: UD


p-value = NS
Impact of ABO matching on OS: UD 8/8 matched

$p = 0.02$
Impact of ABO matching on OS: UD 7/8 matched

- ABO match/18-32
- ABO match/33-50
- ABO match/>50
- ABO MM/18-32
- ABO MM/33-50
- ABO MM/>50

p = 0.008

Months after Transplant

Probability, %
Algorithm of donor search

• Despite the large number of studies, the dearth of randomized trials makes the prioritization of an alternative donor difficult
• The decision may in part reflect the research agenda of the transplantation center because no one source of stem cells is clearly superior to another
• There are themes that can be inferred by the current data to inform a decision
  – Speed = UCB and haploidentical transplantation
  – Cost = haploidentical donors
  – Infection = UCB may be less desirable
  – All mismatched UD are not equal

Natasha Kekre and Joseph H. Antin, July 17, 2014; Blood: 124 (3)
Conclusions

• Donor choice is an evolving landscape
• Good data are the MOST important part of progress
• Selection depends on many factors
  – Factors can ‘trump’ each other
  – What is available!!
• Certainly outcomes are important, but when they are similar other factors come in to play:
  – Clinical studies/trials
  – Local experience/expertise
  – Logistic/cost reasons
  – Patient preference